Applicants thank Examiner LeGuyader for his time and thoughtful comments during a personal interview on March 21, 2000. Applicants understand that the original examiner assigned to the application is on extended leave and that, upon receipt of this response, the application will be transferred to an examiner under the supervision of Examiner LeGuyader. As Mr. LeGuyader suggested, applicants respectfully request the opportunity for a second personal interview or a telephonic interview with the new examiner prior to the issuance of a second office action on the merits, should any issue require further clarification.

Each issue raised in the office action is considered separately below.

Requirement for Restriction

The applicants' provisional election of Group I with traverse was noted. Applicants maintain their traversal of the requirement for restriction. Applicants do not understand how claims that depend from a claim of Group I can be classified separately from the claims of Group I. Allowance of claims in Group I should immediately render allowable any claims that depend therefrom. Applicants respectfully request reconsideration of the requirement for restriction and consolidation of the claims in a single group.

Information Disclosure Statement

The Examiner indicated that the "Cancer Economics" Supplement to the September 1996 Cancer Letter is not found in the file. The document was submitted and considered while the parent application was being prosecuted. For the convenience of the Examiner, a substitute copy of the document is enclosed with this response. Since the document has already been submitted by the applicant, no fee is believed due. However, should a fee be due, please charge the fee to Deposit Account No. 17-0055.

Drawings

The drawings submitted by the applicants were approved by the PTO draftsperson.

Specification

A typographical error noted by the Examiner in the specification is corrected by the amendment above.

Introduction to the Claimed Technology

As a prelude to the applicants' substantive responses to the rejections imposed, applicants wish to point out certain distinctions between the patented method and those disclosed in the pending application. Applicants respectfully suggest that the Examiner did not fully consider these important differences when evaluating the presented claims in view

of either the cited art or the parent patent. Amendments to the claims are intended to highlight and clarify these distinctions.

The pending application is a Continuation-in-Part (CIP) of US 5,780,236 that discloses and claims at least two improvements to the methods of the parent patent and presents claims that differ in approach and scope from those secured in the parent case. The new disclosure in the pending application appears generally between pages 11, line 34 and the end of page 16. The improved methods can be practiced separately or in concert with one another.

The first improved method, described in the specification at page 12, line 26 et seq., is more compact than the methods claimed in the prior case and is particularly advantageous for identifying mutations that induce extreme changes to an index phenotype that can be detected after a first cross. The importance of compacting the method steps in this technology cannot be overstated, since any reduction in the number of mice or the duration of their use represents immediate savings to the user of effort, cost and time.

A first distinction from the methods claimed in the issued patent concerns the genetic makeup of the founder animals used in the breeding methods. In the prior method one breeding step is interposed to generate isogenic founder animals heterozygous only for various mutations induced by the mutagenesis, a holding generation. (See column 5, last full paragraph). Those isogenic founders are then bred with the index animals. In the compact screen, on the other hand, a mutagenized male of the founder strain is mated directly to an animal of the index strain. In this first improved method, there is no effort or need to produce a holding generation of animals heterozygous for the induced mutations. Genetic differences still distinguish the germplasm of the founder and index animals, either because they derive from distinct inbred strains as is described in the paragraph bridging pages 8 and 9 or because they are prepared as described in the improved special case where the founder and index animals are isogenic (see below) with one another.

A second distinction in the compact method derives from the particular choice of mutagenized male animals as the source of possible phenotype-altering mutations and female animals of the index strain. As the application describes on page 21, male offspring of that initial cross (or their frozen gametes) that carry the dominant index allele are backcrossed for just one generation to the index strain to obtain adequate data to determine whether any index-altering mutation was transmitted by an F1 male animal. This is in marked contrast to the more complex methods claimed in the issued patent where the founder animals made as noted above are crossed and then crossed again to produce a Gen2 holding generation for maintaining the gametes of any founder mouse that appears to contribute an index-modifying mutation. The methods of the CIP eliminate the need for the holding generation both by compacting the duration of the screening method and, optionally, by freezing the gametes of F1 male animals. Using this approach, the F1 animals can be bred and then sacrificed for

analysis without fear that any gametes of interest will be lost. Instead, when the data suggest that an F1 male animal may have contained an index-altering mutation, one can retrieve stored gametes from that animal for subsequent breeding.

The CIP application also discloses a second improved method, alluded to above, that reduces genetic background noise in the breeding system. Two embodiments of this so-called isogenic modifier screening method are disclosed on pages 13-15 of the application. Whereas the issued patent considered only using founder and index animals of distinct inbred strains, the second improved method employs animals that are isogenic except insofar as one parent animal carries a congenic dominant allele that confers the index phenotype and the second parent carries only random point mutations relative to a wild-type animal of the background inbred strain. As a direct result of this significant improvement, the effects of the numerous uncontrolled and uncharacterized differences among inbred strains are eliminated as possible factors that might themselves modify the index phenotype. Instead, the isogenic screen of the CIP permits the user to focus only on single point mutations introduced on an otherwise identical background. As in the first improved method, the second method can eliminate the two-stage method for producing founder animals as well as the holding generation for maintaining gametes that may be of interest. In the paragraph bridging pages 14 and 15, the specification describes preparing a "single nucleotide polymorphism (SNP)-marked" index strain for mapping in this improved method, to facilitate distinguishing the index- and founder germplasm. The specification advises that the SNP markers in the index strain can themselves be "phenotypically neutral" so as not to obscure the effects of any mutation introduced from the mutagenized founder animal.

With this background in mind, applicants next respond to each substantive issue raised by the Examiner.

Double Patenting

In rejecting Claims 1, 3, 5, 6, 11, and 25 for double patenting over Claims 1-6 and 9 of US 5,780,236, the Examiner pointed to certain arguable similarities between the pending and issued claims, but incorrectly concluded that the crosses were the same, even though the labels given to each generation were different. For the reasons noted above in connection with the general statements about the technology, applicants respectfully traverse the double patenting rejection.

As noted above, the methods as claimed in the CIP represent a substantial advance in the effectiveness of the method, in terms of reducing the number of animals required, shortening the duration of the method by eliminating entire crosses, and, in certain embodiments, by reducing or eliminating possible interfering genetic differences between the crossed strains. Amended Claim 1 and its dependents relate to the so-called compact screen described above. Certain dependents of Claim 1 incorporate features of the so-called isogenic

screen described above. Amended Claim 11 and its dependents also relate to the isogenic screen. Amended Claim 19 corresponds to animals made according to the method of Claim 1. Amended Claim 21 corresponds to animals made according to the method of Claim 11. Claims 23 and 25 correspond to animals made according to methods disclosed in the prior patent, with no specific recitation of "mice."

The Examiner's focus on such terms as "at least some of" and "half of" or "extreme outlying phenotype" and "outlying phenotype" are not pertinent to the true differences between the issued and pending claims. Precisely because of the improvement brought about by the methods now sought to be claimed, one can, but need not, utilize the cluster method that generally looked to half of the offspring to predict success. Moreover, while the first improved method is not, strictly speaking as strong as the original method, it advantageously permits one to more readily observe and obtain mutations that result in an extreme outlying phenotype. The meaning of that phrase for purposes of §112 is discussed below.

The Examiner also raised an issue of applicants' use of the terms "carrying random point mutations" in Claim 11 and "heterozygous only for random point mutations" in issued Claim 1. Here the Examiner has confused heterozygosity of the allele that confers the index phenotype with heterozygosity for random point mutations, one or more of which may be a sought-after index-phenotype-altering mutation. It simply makes no sense to use this erroneous distinction as a basis for a double patenting rejection.

Because of the shortcomings in the Examiner's double patenting rejections for the method claims, the corresponding double patenting rejection for the non-human animal claims can, likewise, not stand.

For all of the reasons noted above, applicants respectfully suggest that granting of the claims in the pending application will not unfairly extend the patent rights to US 5,780,236, but rather that these claims cover a substantial new and distinct invention for which the applicants are entitled to a complete patent term.

Rejections Under 35 U.S.C. §112, first paragraph

Claims 1-6, 11-16, 19-23 and 25 were rejected under §112, first paragraph for overbreadth. The applicants respectfully traverse the rejection and point out that the method clearly states the requirements for any animal that can be used effectively in the method. Thus, for any animal species for which suitable inbred animals are available, the method is enabled, notwithstanding the breadth of the claims. The procedures themselves are breeding steps; invention resides in manipulating those steps to achieve the desired result.

As far as is known to the applicants, all known non-human animals encompassed by the claims strictly follow the rules of genetic inheritance. Thus, it is certainly within the ability of one skilled in the art to utilize the claimed invention with any suitable animal that meets the requirements of the claims. To limit the applicants to coverage for a method using

only mice of the exemplified embodiments would unduly limit the value of the claims since others in the field would immediately look to other strains or other animals in which to perform the methods.

Reconsideration of the merits of this rejection and withdrawal of the rejection are respectfully requested.

Rejections Under 35 U.S.C. §112, second paragraph

The Examiner rejected Claims 1-6 and 11-25 for use of the phrase "at least some of" or the phrase "some of." The phrases no longer appear in the claims. For clarity, applicants have replaced the phrases with "at least one."

The Examiner further rejected the claims for the use of the allegedly indefinite term "extreme," noting the applicants' definition of the term "extreme outlying phenotype" on pages 12 and 13 of the specification. The indefiniteness is not understood by the applicants. As the applicants pointed out in the specification, one can only know the meaning of the term "extreme" when placed in the context of the particular phenotype for which one seeks modifiers. Applicants simply cannot incorporate the limitation to a particular phenotype into the broadest claims. To do so would be to diminish the value of the claims to that which has already been done by the applicants. Instead, the applicants here enable a method fully suited to obtaining modifiers for a whole host of phenotypes. The Examiner's attention is directed to the only full paragraph on page 7 which lists a number of kinds of phenotypes that can be studied and for which modifiers can be obtained using the method. Upon considering the list noted in the specification, the Examiner will understand both that it is difficult if not impossible to state a particular percentage as indicative of an extreme outlying modification and also that the skilled artisan can readily do so once a suitable phenotype has been selected. The Examiner also questioned the terms "enhancing effect" and "suppressed phenotype" in Claim 14. The Examiner's attention is directed to the second full paragraph on page 14 where this aspect of the invention is described. The terms "enhanced" and "suppressed" are used as throughout the application, namely where the phenotype is increased or decreased. The precise nature of that enhancement or suppression will again depend upon the nature of the index phenotype. The subject matter of Claim 14, in particular, relates to situations where the genetic background on which the crosses are performed has an effect upon the phenotype itself. Thus, to use the example of the exemplified embodiment, one can perform the crosses of the method on a genetic background that itself contributes to higher tumor counts, thereby making it easier to detect animals having a markedly lower tumor count. The converse is also true -- where the genetic background markedly reduces the number of tumor counts, it becomes easier to detect animals having a high tumor count.

The other issues raised by the Examiner under §112, second paragraph are addressed in the amended claims.

Rejections Under §102

The rejections under §102(a) are traversed. Bilger et al. (1996) does not teach a method for identifying the *Min* allele that modifies the multiple intestinal neoplasia phenotype in B6-*Min* mice. Instead, Bilger et al. sought modifiers of the *Min* phenotype as have the applicants. One of the named inventors is a co-author of the Bilger paper. Bilger et al. is merely background to the methods and products of the present invention. In describing efforts to find modifiers of *Min*, Bilger et al. describe crossing B6-*Min* mice to various inbred strains. In no instance does Bilger describe crossing B6-*Min* mice either to mutagenized animals or to isogenic animals containing only random point mutations as recited in the claims. Thus, while Bilger et al. tried to obtain modifiers of *Min*, the authors approached that problem using entirely different methods unrelated to those of the pending application or its parent. The major point is that the work of Bilger et al. describes polymorphic modifiers obtained from prior work in the inventors' laboratory. Such polymorphic modifiers present significant problems for identifying the molecules responsible for altering an index phenotype. In contrast, the methods of the present invention present more elegant solutions for obtaining modifications induced by single point mutations which are much easier to characterize.

The rejections under 35 U.S.C. §102(b) are also traversed. The applicants reiterate that the index phenotype of the present invention is a phenotype that can be modified quantitatively by an additional segregating mutation. The Examiner asserts that T/t is an index phenotype. This is not true. T/t was a compound genotype; T was a genetic marker used for mapping and t prevented recombination in the region. Shedlovsky et al. looked for and found qualitative mutations (recessive lethals) linked to the Brachyury mutation, T. The results of that screen were qualitative: the mice were either alive or dead. Here, in contrast, one can observe subtle gradations in a phenotype, as shown in the working example.

The Examiner asserts that the T/t mice are an index inbred mouse strain. This is not the case. Claim 1 requires the index inbred mouse strain to carry a dominant allele at a locus known to confer an index phenotype, but there was no such allele in the T/t mice of Shedlovsky. Nor was there any trait in those T/t mice that would have been modified quantitatively by a cross with mutagenized BTBR mice. The Examiner has also asserted that the cross between BTBR and the T/t mice yields "gen1, the founder strain, heterozygous for point mutations." The Examiner has merely sought to use the words of the claim without attending to the underlying genetics. The cross described by the Examiner is simply a different cross from that of Claim 1. It is believed that the Examiner's inaccuracy arises from a misunderstanding of the term "index." The observations above should clarify this point.

In summary, because Shedlovsky does not disclose the basic cross of Claim 1, it cannot anticipate the rejected claims. Reconsideration and withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §103

Claims 2, 5 and 18 were rejected as unpatentable over Shedlovsky in view of Moser and Dietrich. For the reasons noted above, Shedlovsky does not teach the crosses of the claimed invention as asserted by the Examiner and, accordingly, does not yield mice that read on Claim 18. Moreover, Moser et al., also from the same laboratory, merely describes the *Min* allele, while Dietrich discloses a polymorphic modifier of *Min*, now known to be complex.

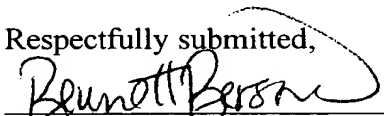
Particularly because of the short comings in Shedlovsky, but also because of the complete absence from the Dietrich and Moser papers of any disclosure relating in any way to the identification of a modifier induced by random point mutations, applicants respectfully traverse the rejections under §103. Indeed, Dietrich says that "analysis of modifier loci has rarely been employed in mammals, because large scale mutagenesis to isolate modifiers is not practical..." (Dietrich et al., Discussion, p. 635, col. 2).

Applicants also point out that Moser does not disclose using preserved gametes from mouse germ line mutations. For these same reasons, the mouse of Claim 18 cannot be rendered obvious by the cited references, since none has the characteristics of the mouse that results from the claimed method.

Having responded to each ground of rejection, applicants respectfully request reconsideration of the merits of this patent application.

A petition for one month extension of time is submitted with this response so the response will be deemed to have been timely filed. Should any other extension of time be due, in this or any subsequent response, please consider this to be a request for a suitable extension and a request to charge the fee due to Deposit Account No. 17-0055. Likewise, should any other fee be due in this or any subsequent response, please consider this to be a request to charge the fee to the same Deposit Account.

Respectfully submitted,



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